Federal Institute for Drugs and Medical Devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Estimands: One way Forward

1st EFPSI Workshop on Regulatory Statistics, Basel

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Disclaimer

The views expressed in this presentation are the personal views of the speakers and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA, one of its committees or working parties, or the BfArM .

No document yet formally reviewed at EMA.

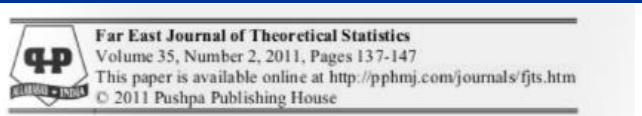
Some slides were developed by colleagues in the ICH E9(R1) Expert Working Group.

ICH E9 (R1)

First major ICH Statistical Document in over a decade

Estimands – fun facts

- It is on Wikipedia since 22nd October 2014
  - Although short page with 3 references and only in English
- 43 hits on PubMed (as of 2nd September 2016) – 20 since 2014
- National Academy of Sciences paper* in 2010 has 99 mentions of estimand



First Google Image

THE INSTRUMENTAL VARIABLE ESTIMAND AS AN AVERAGE CAUSAL EFFECTS UNDER PARTIAL COMPLIANCE

A. FORCINA
Dipartimento di Economia
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First Google image not in English

推定値（Estimand）とは

- 臨床試験の推定値(Estimand)には、①母数（平均値変化の群間差など）、②時点・治療期間、③アウトカム、④対象集団、⑤治療非継続時のフォローアップデータの適格・除外などを含む。
- 介入研究における推定値について考える上で、有効と有用を分ける

→有効(efficacy)：治療を継続的に受けた時に、エンドポイントで期待される効果

→有用(effectiveness)：実際に治療を受けた時（中断する人もいる状況）の治療効果（有効だが有用ではない治療もありえる）。

Mallinckridt(2013)"Preventing and Treating Missing Data in Longitudinal Clinical Trials"

*National Research Council. (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials.

Outline

- Update on ICH process and E9(R1) Addendum development
- Background on the regulatory discussion
- Impact on EU regulators

ICH

International **Council** for **Harmonisation** of Technical Requirements for Registration of Pharmaceuticals for Human Use

…Previously Conference on used in place of

Council for

…See www.ich.org for more details

…also, see next slide

History of ICH

- Begun officially in 1990 (informally in 1989)
- Originally three regions in ICH
- Europe (EU), U.S. and Japan
- Regulators and Industry at the table
- Developed guidelines recognised by the Regulators
- Recent reorganisation… more regulators on board. New assembly (Oct. 2015)

"E" is for Efficacy

- E3 Clinical Study Reports
- E6 Good Clinical Practice (Revision 2, public consultation over)
- E8 General Considerations for Clinical Trials
- E9 Statistical Principles for Clinical Trials (February 1998)
- E10 Choice of Control Group in Clinical Trials
- E11 Clinical Trials in Paediatric Population (Revision 1 on-going, soon to be published)
- E17 Multi-Regional Clinical Trials (under public consultation)

E9(R1) Expert Working Group

- Industry representatives from Europe, Japan and US
- Regulators from Europe, US, Japan, Canada, Taiwan, Brazil (plus Australia)

- Rapporteur: Rob Hemmings, MHRA
- Regulatory Chair: Estelle Russek-Cohen, FDA
- EU Regulatory Deputy Topic Leader: Frank Pétavy, EMA
- EU Industry representatives: Frank Bretz (Novartis), Chrissie Fletcher (Amgen)

Steps in the ICH Process

ICH Review Process

- Step 1: so called Technical Document, then becomes Addendum
- Step 2: approval of E9(R1) Addendum
- Will include:
  - Original E9 with comments/changes (TBC)
  - Addendum on estimands and sensitivity analyses
  - Supportive material (TBC) on ICH website
- Posted on EMA website for consultation - very similar to a draft EMA guideline
  - Consultation timelines will vary across regions (see E17 for example) – 3mo, 6mo, longer?
- Step 4: Final guideline - recognised by EMA, FDA, etc.

Ongoing work in ICH group

- Detailed and complex conceptual and technical discussion to ensure **methodological rigour**.
- Attention that the 'statistical principles' being delivered are appropriate **across therapeutic indications and experimental situations**.
- '**Due diligence**'
    - Technical correctness
    - Practical consequences
    - Multi-disciplinary input
- **Case studies** to support **local consultations** and broader understanding of our message
- Drafting of the technical document and proposed text to **update ICH E9**.
- Determine the need for, and content of, a **technical appendix** to the addendum

What is an estimand ?

Estimand = that which is being estimated

- latin gerundive *aestimandus* = to be estimated
- simply speaking: the precise (distributional) parameter to be estimated
- However:
  - the parameter may not always be given easily
  - may be a (complex) function of other parameters from a multivariate distribution

Target of the estimation function *f*

- evaluate properties of *f* w.r.t. the estimand θ
- e.g. E { *f*(data) } $\approx \theta$

Early discussions on missing data imputation (1)
(*pros and cons*)

LOCF

- traditional (allegedly) conservative primary analysis
- can be anticonservative, especially in a progressive disease
- LOCF leads to biased estimates, underestimates the variance
- precise target unclear

MMRM (mixed model repeated measures)

- MMRM works fine under MAR (missing at random)
- missing not at random assumption (MNAR) not determinable
- MAR may not be valid
- often similar to PP analysis
  - depends on MMRM definition
  - drop-outs contribute via covariates

Early discussions on missing data imputation (2)

Multiple imputation

- may consider MNAR
- displays proper variability
- may use conservative assumptions / identifying restrictions on unmeasured post drop-out data (e.g. placebo MI, jump-to-reference, etc.)
- many different (unverifiable) MNAR assumptions
- may not be fit for primary analysis
  - analysis model ≠ data generation model
  - target parameter to be estimated ?

Early discussions on missing data imputation (3)

Return to MMRM ?

- Properly defined and powerful primary analysis
- Many possibilities
- Which MMRM?
  - Strict regression models with few degrees of freedom
    → robustness may be questionable
  - General model
    - unstructured covariance
    - discrete treatment-by-visit interaction
      → drop-outs not (less) informative
- **Target estimand:**
  - **Efficacy if all patients were treated as directed**
  - **Does not target effect under actual compliance**

Example: Simulation of a depression trial with retrieved data

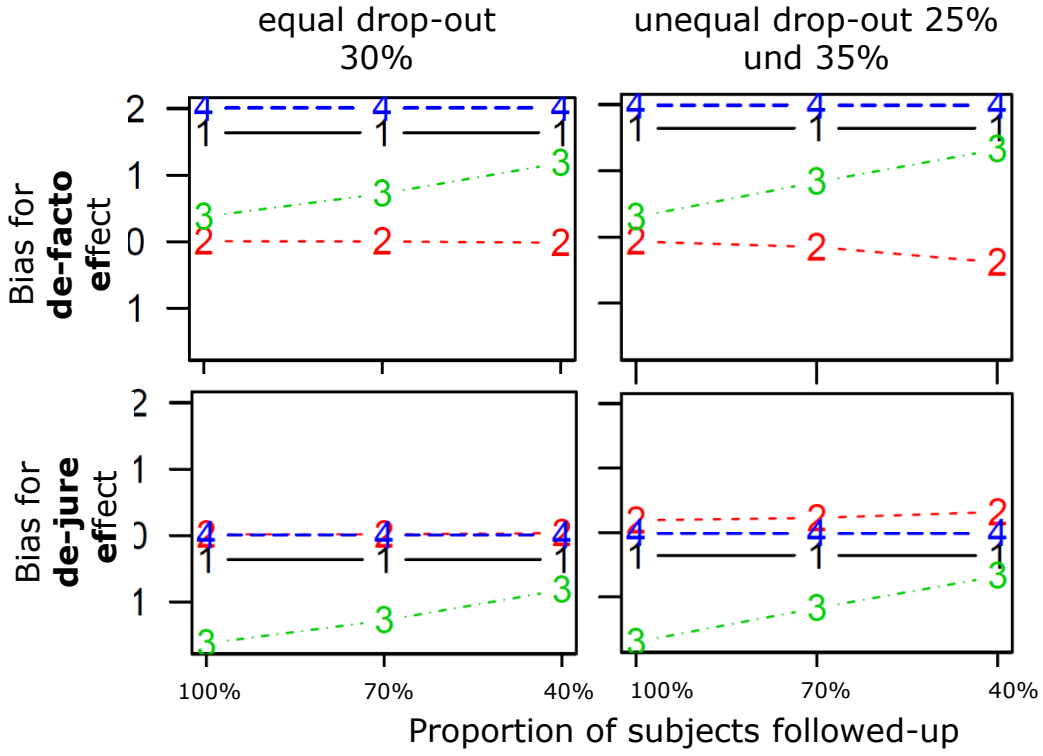
- Longitudinal data (Hamilton Score)
- Non-adherence: Treatment discontinuation
- Some data were collected after treatment discontinuation
- Different drop-out mechanisms
  - treatment dropout (TD)
  - analysis dropout (AD)
    - AD time ≥ TD time
    - “retrieved data” from TD to AD

Leuchs et al (2014). *Statistics in Medicine 33*

- Data generation
  - according to a two-piece linear mixed model, selection model for TD, exponential time to AD

Example: Bias of different analysis strategies for de-jure and de-facto estimands

- true de-jure effect = 2
  (difference if all subjects adhered)
- true de-facto (treatment policy) effect = 0
  (difference in all subjects)
- Analysis strategies
- 1: Multiple Imputation (Pattern-Mixture Model)
- 2: Joint Model of drop-out and outcome
- 3: Mixed Model, all data
- 4: Mixed Model, only data under treatmer



Leuchs et al (2014). *Statistics in Medicine 33*

EMA/BSWP Workshop, February 2016

European Regulators only - Attendees from NCAs, CHMP, PDCO, SAWP and EMA

Mix of clinicians and statisticians – key decision-makers in EU network

Part of E9(R1) local consultation - 2nd meeting after 1-day PSI meeting in Uxbridge, September 2015

Objectives:

- inform colleagues
- engage non-statisticians
- reflect on examples

Mix of plenary sessions and breakout sessions (Cardiovascular, Oncology, CNS and Respiratory diseases)

Impact so far of E9(R1) on EU regulators (1)

- Publications from EU regulators
  - Estimation of the treatment effect in the presence of non-compliance and missing data (Leuchs et al., *SiM* 2014)
  - Choosing Appropriate Estimands in Clinical Trials (Leuchs et al., *Therapeutic Innovation & Regulatory Science* 2015)
- Increase of mention of estimands in regulatory submissions
  - Scientific Advice packages, steady increase since 2013
  - Also appearing in MAA pre-submission meetings and in MAA dossiers

Impact so far of E9(R1) on EU regulators (2)

- Recent EMA therapeutic guidelines refer to estimands" or the "scientific question of interest"
  - Draft guideline on the clinical development of medicinal products intended for the treatment of **pain**, 21/12/2015
  - Draft guideline on the clinical investigation of medicines for the treatment of **Alzheimer's disease and other dementias**, 28/01/2016
  - Guideline on clinical evaluation of medicinal products used in **weight management**, 23/06/2016
- Future therapeutic guidelines
  - Is it the right place for specific estimand considerations?
  - Under which part/section? Endpoints, statistical considerations?

Impact so far of E9(R1) on EU regulators (3)

- Increasing number of scientific advice procedure with questions on estimands, e.g.
  - Pain, diabetes: How to treat data under rescue medication ?
  - Asthma (count data): How to consider different treatment periods ?
  - Oncology: How to consider treatment cross-over ?
  - …
- Increasing discussions with clinicians
  - Workshops, advice procedures: Getting aware of different estimands

Next Steps

- Another estimand session today!
- More case studies, examples, discussions, publications needed
  - Practice helps reflection (and sometimes makes perfect)
- Next Stop: Osaka, 4-9 November
- EMA Industry Workshop 2017/2018 (TBC)

Thank you for your attention

Further information

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BACK-UP SLIDES

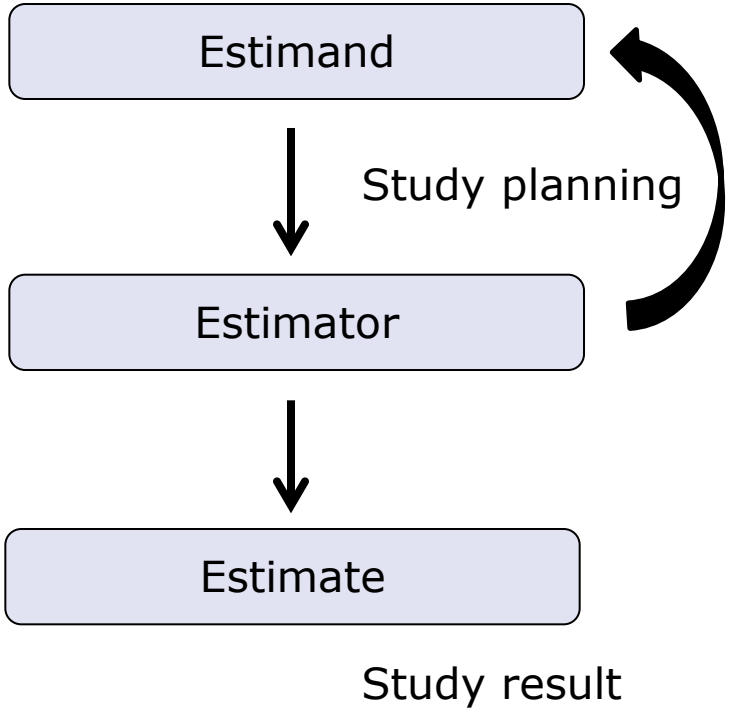
Distinguish 'target of estimation' and 'method of estimation'

Estimand framework helps distinguishing between

- target of estimation (estimand)
- method of estimation (estimator)

Especially in the context of 'missing data' the estimand and method of estimation are often confused

However, estimand framework applies to a broader setting than missing data



Some Comments

Writing this guideline is a challenge:

- **Estimand** + **Estimation function ("estimator")** needs to be carefully planned. Not one size fits all and the guideline will point to a framework; companies and regulators will need to discuss.
- This is far better than trying to figure out what was meant after the study is over.
- A subgroup is working on impacts on protocols.

Estimand – A proposed definition

An estimand reflects what is to be estimated to address the scientific question of interest posed by a trial.

The choice of an estimand involves:

- **Population of interest**
- **Endpoint of interest**
- **Measure of intervention effect**

Estimands that are of regulatory interest

While no concrete recommendations will be made in ICH E9(R1), as these can only be case-specific, general principles for the choice of estimands will be discussed

1. **Clinically meaningful**
2. **Randomization based**

- Allow for inference based on all randomized patients

3. **Minimal and plausible assumptions**

- Allow for inference where for every randomized patient the outcome used in the analysis was actually observed and is imputed using minimal and plausible assumptions